Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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APPROVED
By Andrea Sutherland, MD, MSC, MPH at 5:28 am, Mar 16, 2012

From: Andrea Sutherland, MD, MPH, MSc
Special Assistant to the Director of the Division of Epidemiology, OBE/CBER/FDA

To: STN 125126

Through: David Martin, MD, MPH
Director of the Division of Epidemiology, OBE/CBER/FDA

APPROVED
By David Martin, MD, MPH at 6:04 pm, Mar 15, 2012

Subject: Gardasil Pediatric Utilization and Safety Review for the Pediatric Advisory Committee Meeting — May 7-8, 2012

Sponsor: Merck & Co., Inc.

Product: Gardasil, Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant

Pharmaceutical form: 0.5mL sterile liquid suspension for intramuscular injection in a vial or pre-filled syringe, containing approximately:

20 mcg of HPV types 6 and 18 L1 proteins
40 mcg of HPV types 11 and 16 L1 proteins
225 mcg amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant
9.56 mg sodium chloride
35 mcg sodium borate
0.78 mg L-histidine
50 mcg polysorbate 80
<7 mcg yeast protein

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1. INTRODUCTION

On June 8, 2006, the US Food and Drug Administration approved Gardasil, the first vaccine against the human papillomavirus (HPV). Gardasil was initially licensed for females aged 9–26 years for the prevention of cervical cancer, precancerous lesions and genital warts caused by the vaccine serotypes (6, 11, 16 and 18). The indication for the prevention of vulvar and vaginal cancer was approved on September 12, 2008. On October 16, 2009, Gardasil was approved for the prevention of genital warts caused by HPV 6/11 in males 9 - <27 years of age. On December 22, 2010, Gardasil was approved for the prevention of anal intraepithelial neoplasia 1/2/3 and anal cancer in both males and females 9 - <27 years of age. These two recent approvals for additional indications for Gardasil are the triggers for this pediatric utilization and safety review and Pediatric Advisory Committee. The 2009 approval introduced the vaccine to the male population and prompted changes in the recommendations for clinical use promulgated by the Advisory Committee on Immunizations and Practices (ACIP). On October 22, 2009, ACIP approved the "permissive" use of Gardasil in males and provided coverage under the Vaccines for Children (VFC) program. Note the addition of the indication for the prevention of anal cancer in 2010 did not alter the vaccine's composition, administration, or female target population and did not result in changes to the recommendations of use in females. On October 25, 2011, the ACIP recommended use in males and thus made Gardasil part of the routine recommended vaccination schedule in males.

2. OBJECTIVES

The objective of this memorandum and the accompanying presentation to the Pediatric Advisory Committee (PAC) is to provide a targeted safety review for Gardasil, focusing on the time frame following approval of Gardasil for the prevention of genital warts due to HPV 6/11 in males on October 16, 2009 up to one year following the approval for the prevention of AIN 1/2/3 and anal cancer in males and females, ending in December 22, 2011. The purpose is to determine if there is evidence for any new safety concerns that might have emerged as a result of using the vaccine in a male population, or if any new safety concerns have arisen during the noted time period in the general, predominantly female, population of vaccine recipients. In addition, this memorandum will briefly review previously identified safety issues and the results of postmarketing studies to date. Lastly, this memorandum will review the planned and ongoing postmarketing studies for Gardasil.

3. SOURCES OF SAFETY DATA

3.1 Vaccine Adverse Events Reporting System (VAERS)

- VAERS reports among children aged 0 – 16 years vaccinated between October 16, 2009 and December 22, 2011

3.2 Manufacturer's Postmarketing Commitments (PMC)

- Merck's active surveillance program for females in a managed care organization (final revised results)
- Merck's pregnancy registry, 5th Annual Report

3.3 Vaccine Safety Data Link (VSD) Study on Gardasil

4. LABELING CHANGES

There were no labeling changes for Gardasil regarding safety from October 16, 2009 to December 22, 2011.

5. DOSES DISTRIBUTED Merck reported that an estimated 15,300,000 doses were distributed in the United States between October 16, 2009, and December 22, 2011. Prior to this period, approximately 28 million doses of Gardasil were distributed in the US since licensure in June 2006. There are no

available data of the number of doses administered to specific groups stratified by age and sex. The 2010 National Immunization Survey estimated that approximately 32% of the female population, aged 13-17) had received the complete series of three doses. (http://www.cdc.gov/vaccines/stats-surv/nisteen/data/tables_2010.html)

6. BACKGROUND SAFETY INFORMATION

The purpose for this brief overview is to provide background information and context, given that Gardasil has been marketed for almost 6 years since licensure in June 2006.

6.1 Previously Published VAERS Safety Review (June 1, 2006 – December 31, 2008)

12,424 VAERS reports received from June 1, 2006 through December 21, 2008 have been previously reviewed and published. (Slade) The report covers the first 2.5 years of marketing, during which an estimated 23 million doses were distributed in the United States. See the Gardasil PAC memorandum dated October 11, 2010, presented on December 8, 2010 for a thorough review of this study. In summary, approximately 94% of these reports were non-serious. The most frequently reported adverse events were syncope, dizziness, nausea, headache, and injection site reactions. The overall safety profile described in VAERS was consistent with prelicensure data, with two notable exceptions, syncope and venous thromboembolic events (VTEs) were reported more frequently after Gardasil than other vaccines. VTEs usually occurred with concomitant use of oral contraceptives (OCPs).

6.2 Merck's Regulatory Postmarketing Commitment : Active Surveillance, Observational Study in Females

A postlicensure commitment for active surveillance of Gardasil in females aged 9 – 26 years was made by Merck upon initial licensure. The study was conducted in Kaiser Permanente (KP) Northern and Southern California between August 2006 – March 2008. A revised final report was submitted to the FDA in December, 2010. A total of 346,972 Gardasil doses were evaluated. The primary study population consisted of 44,001 females aged 9–26 years who received 3-doses of Gardasil. In total, 189,629 females of any age received ≥1 dose, 51% of them were aged 9 – 15 years. Safety signals were identified for syncope and cellulitis. The incidence rates were estimated as 6.6 cases of syncope per 100,000 doses on the day of vaccination, and 13.5 cases of cellulitis per 100,000 doses, occurring 1 to 14 days after vaccination. Both conditions have been observed following other vaccinations, and are likely attributable to the method of administration (injection) and the target population (adolescents, which have the highest rates of syncope), rather than the vaccine itself. No other safety signals were noted. Pregnancy surveillance had limited results as not all identified cases were exposed or even pregnant. Nonetheless, from the available data, no unusual patterns in pregnancy outcomes or congenital birth defects were identified. There were no safety signals for the pre-specified autoimmune diseases. (Chao)

6.3 Merck's Pregnancy Registry:

As there are no adequate well-controlled studies in pregnant women, Gadasil is not recommended for use in pregnant women and is a Category B product.
Merck's pregnancy registry collects spontaneous reports of pregnancy exposures. Exposure is considered within one month prior to the date of onset of the last menstrual period (LMP) or at anytime during the pregnancy. Reports are classified and sub-analyzed as "prospective", received before the birth, or "retrospective" when received after the birth and the outcome is thus known. The 5th Annual Report on Exposure during Pregnancy from Merck Pregnancy Registry for Quadrivalent Human Papillomavirus (Types6,11,16,18) Recombinant Vaccine [Gardasil/Silgard] covers the period from first approval (June 1, 2006) through May 31, 2011. The study included 4424 women, 2286 prospective reports made during pregnancy with outcomes followed when feasible, and 348 retrospective reports submitted after the birth. The spontaneous abortion rate was 6.4 per 100 pregnancy outcomes, noting that the background sAB rate is approximately 15%. There were 12 fetal deaths, some with clear contributing factors, resulting in a rate of 0.9 per 100 births, compared to a background rate of 0.62-1.0 per 100.

Congenital anomalies were varied in type, etiology, gestational age at exposure, with no clinical or temporal clusters, suggesting that they were not related to vaccine. This is an ongoing study anticipated to end in 2012. In sum, the overall rate of congenital anomalies and miscarriages was within estimated background rate. A review of congenital anomalies and deaths did not identify any unusual patterns.

Reports of Fetal Deaths and Congenital Anomalies to the Pregnancy Registry Among Females ≤ 16 Years

Maternal age (years)	Report summary	Notes
12	Fetal death 21 wks	Rh incompatibilty
14	Fetal death, GA unknown	
15	Fetal death 24.3 wks	
16	Fetal death 37 wks	HTN, pre-eclampsia
15	Gastroschisis	
16	Pulmonary valve stenosis	
14	Atrial septal defect	
15	Atrial septal defect	
15	Polydactyly	
14	Hydrocephalus	
16	Pyelocaliectasis	
15	Spontaeous abortion	
15	Hypospadias	
16	Amelia	
16	Congenital uterine anomaly	Lysosomal storage disease

6.4 Vaccine Safety Data Link (VSD) Postlicensure Study of Gardasil in females

The VSD is a collaborative effort between CDC's immunization safety office and eight healthcare maintenance organizations across the United States. It was established to study vaccine safety concerns and comprises approximately 3% of the US population in a large linked administrative database. The VSD conducted active surveillance for Gardasil, using rapid cycle analyses, between August 2006 and October 2009, in seven managed care organizations. During this time, 600,558 doses were analyzed in females aged 9–26 years, and 416,942 among females aged 9–17 years. A total of 9 health outcomes were pre-specified and analyzed: Guillain-Barre syndrome (GBS), stroke, appendicitis, seizure, syncope, allergic reactions, pancreatitis, anaphylaxis and VTE. Syncope occurred after all adolescent vaccinations, including Gardasil. Venous thromboembolism (VTE) was found to have a non-statistically significant relative risk (RR) of 1.98; and, other recognized risk factors (including oral contraceptive use, coagulation disorders, smoking, being overweight) were noted in the five cases of VTE. Upon chart review, the one case of Guillain-Barre Syndrome was found to be not incident. A case-centered analysis of appendicitis showed no statistical association. There was no statistical association for seizures, whether recurrent or new onset. Allergic reactions and anaphylaxis were found at a rate of 1.7 cases per million doses administered, which was similar to other vaccines. There were no statistically significant safety signals identified for the pre-specified events which when identified after vaccination often had other established contributing factors. The published manuscript recommends further studies of VTEs after Gardasil. (Gee)

7. Pediatric Advisory Committee Safety Review: October 16, 2009-December 22, 2011

The following is a review of VAERS events reported with vaccination date between October 16, 2009 and December 22, 2011. (The VAERS data was updated and last accessed on March 5, 2012.)

7.1 Classification of VAERS Reports by Age and Category

7.1.a Classification of VAERS Reports by Age and Category – Female and Male

Females and Males	Serious*		Deaths		Non-serious		Total	
	US	Total**	US	Total	US	Total	US	Total
>27 years	3	7	0	0	40	53	43	60
17-26 years	88	128	6	6	1089	1128	1177	1256
9-16 years	123	559	4	8	1882	2096	2005	2655
0-9 years	0	0	0	0	20	21	20	21

*** "serious" includes: Death, life-threatening experiences, inpatient hospitalization or prolongation of hospitalization, or persistent disability**

****Total = US plus foreign reports**

Of the total 2005 reports for 9-16 year olds, 123 (6%) were serious. Of the total 2676 global reports, 2025 (76%) were US reports. There were a total of 8 death reports, 4 US and 4 foreign. There were 20 US reports of use in 0-8 year olds, although Gardasil is indicated only for 9-26 year olds.

Of the total 2025 US reports, 427 (21%) for 0-16 y/o were in males.

7.1.b Classification of VAERS Reports by Age and Category – Male

Males	Serious		Deaths		Non-serious		Total	
	US	Total**	US	Total	US	Total	US	Total
>27 years	1	1	0	0	2	2	3	3
17-26 years	15	15	2	2	124	124	139	139
9-16 years	25	25	3	3	394	396	419	421
0-9 years	0	0	0	0	8	8	8	8

*** "serious" includes: Death, life-threatening experiences, inpatient hospitalization or prolongation of hospitalization, or persistent disability**

****Total = US plus foreign reports**

As this PAC was in part triggered by the new indication for use in males, this review will also present data for males separately. Of the total 419 reports for 9-16 year old males, 25 (6.0%) were serious, a similar rate as for all Gardasil reports, and 3 reports of death. All reports except for two were domestic.

For the remainder of this section, for purposes of the Pediatric Advisory Committee, the analyses will focus on VAERS events reported among children aged ≤ 16 years.

7.2 VAERS Reports of Death after Gardasil for children under 16 years of age

Reports of Death after Gardasil for children under 16 years of age

VAERS ID number	Age. sex	Onset of death after vaccination	Concomitant vaccines administered with Gardasil	Cause of death	Notes
405821	15 y/o, male	28 days	None	Congenital subaortic membrane, reactive airway disease cardiac and respiratory failure	15 y/o m, with h/o asthma and unspecified "cardiac history", on Lipitor, died suddenly 28 days after Gardasil vaccination while playing hockey.
403759	10 y/o, male	8 days	Menactra, Hep A, and Tdap	Acute asystole, myocarditis, hypoxic encephalopathy	No reported medical history except for fall at football practice
442402	15 y/o, male	3 days	Menactra, Tdap	Seizure	H/o pervasive developmental disorder and intractable epilepsy
430780	14 y/o, female	14 days	Fluzone	Sudden cardiac death	Cardiac insufficiency, early cardiomyopathy
441365	14 y/o, female	9 days	None	Acute leukemia and cerebral hemorrhage	Calf pain and pupura, headaches, admitted to hospital with cerebral hemorrhage and acute leukemia
387594 (foreign)	11 y/o, female	96 days		Not reported	
393871	15 y/o, female	3 days		Suicide	
419174	15 y/o, female	3 days		Renal and cardiac failure	History of "long standing health problems". One month h/o hemoptysis prior to vaccination

No patterns have been identified among the reports of deaths after Gardasil that suggest a relationship between vaccination and the reported cause of death.

7.3 Serious US VAERS Reports after Gardasil for Children 9 ≤ 16 Years

Most Frequently Reported MedDRA Preferred Terms Among Serious US VAERS Reports

There were 125 US serious VAERS reports. The table below lists the most frequently reported MedDRA Preferred Terms among 9-16 year olds. (There were no serious reports for under 9 years of age.)

MedDRA Preferred Term	Number of Events Males and Females	Listed in Label/Notes
Headache	89	Yes
Dizziness	56	Yes
Nausea	51	Yes
Fatigue	42	Yes
Pyrexia	42	Yes
Vomiting	42	Yes
Abdominal pain	41	Abdominal pain upper listed in clinical trial data in males
Asthenia	38	Yes
Malaise	35	Yes
Loss of consciousness	34	Syncope
Paraesthesia	30	No
Syncope	30	Yes
Convulsion	29	Tonic-clonic movements with syncope

Most Frequently Reported MedDRA Preferred Terms Among Serious US VAERS Report in MALES

MedDRA Preferred Term	Number of Events Males	Listed in Label
Abdominal pain	9	Abdominal pain upper listed in clinical trial data in males
Headache	7	Yes
Abdominal pain upper	5	Abdominal pain upper listed in clinical trial data in males
Fatigue	5	Yes
Nausea	5	Yes
Asthenia	4	Yes
Convulsion	4	Seizures, syncope associated with tonic-clonic movements
Malaise	4	Yes
Pyrexia	4	Yes
Vomiting	4	Yes
Chest pain	3	No

Medical Officer Review of Serious VAERS Reports

All serious cases have been re-reviewed. The following is a table is of case summaries assigned by a medical officer for US serious non-fatal VAERS reports for 9-16 year olds who were vaccinated between October 16, 2009 and December 22, 2011, divided by sex.

Event Summary	Number females	Number males	Notes
Syncope	15	4	6 – convulsive syncope 3- traumatic head injury
Guillain-Barre	4	2	
Seizures	9	2	
Other neurologic	10	3	chorea, encephalopathy, dystonia, asthenia
Transverse Myelitis	1		
Myasthenia Gravis	1		
Headache, Migraine	11		
Psychiatric	5		Depression, psychosis, possible conversion disorder
Rheumatoid arthritis	4		
R/O MS or SLE	1		
Bell's Palsy	1		
Optic Neuritis	1	1	
Idiopathic thrombocytopenia	3		
Irritable bowel syndrome	1		
Severe abdominal pain/GI	6	1	
Appendicitis	2	1	
Pancreatic cysts		1	
Pancreatitis		1	
Diabetes	5	1	Male- Diabetic Ketoacidosis
Thromboembolic events	1		Subclavian venous thrombosis

Event Summary, cont.	Number females	Number males	Notes
Arrhythmia		1	
Acute Leukemia	1		
Cellulitis	2	1	
Allergic Reaction	1		
Serum sickness	2		
Stevens Johnson Syndrome		1	H/O SJS
Recurrent Pneumothorax		1	Pre-existing medical conditions
Arrhythmia		1	
Vaccination during pregnancy	2		
Other (sinusitis, fever, viral illness)	8		
Total (slide 18, 19, 20)	97	22	119 non-fatal (+ 4 fatal = 123 SAEs)

The types of adverse experiences most frequently reported in the postmarketing period have been consistent with those observed in clinical trials and with what is expected in a non-vaccinated, background population in this age range. Although syncope was reported in the clinical trials, its association with injuries and/or tonic-clonic movements was a new safety signal detected by VAERS. As a result, the package label was amended to highlight syncope, convulsive syncope and related traumatic injury, to appropriately alert patients and their health care providers. Importantly, the label also describes available measures that can be taken to prevent and initially manage syncope appropriately, including an iteration of the current guideline of waiting 15 minutes after vaccination, and placing the patient in Trendelenberg position to restore cerebral perfusion if syncope does occur.

There were six cases of Guillain-Barre Syndrome (GBS) reported after vaccination, all within the established 42 day risk window. In some of these reports, other vaccines, including influenza vaccines, were administered, and/or viral illnesses were noted. The reporting rate for GBS would be approximately 6/15,300,000 doses, or 0.4 per million doses distributed, which is below the expected background rate. The large study in the VSD did not detect any safety signals for GBS. Evaluation of the serious reports does not demonstrate any unusual clinical or temporal patterns. All of the most frequently reported preferred terms listed above are now listed in the package label.

While VAERS is a timely national passive surveillance system, the limitations of VAERS must be noted: under-reporting, inability to calculate incident rates, incomplete or inconsistent data, reporting or coding errors, bias in reporting events which are temporally proximal to vaccination, influenced by media and public information. In most analyses, VAERS data are not sufficient to establish causality, but it serves a vital purpose for signal detection, hypothesis generation, and AE reporting trend analysis.

7.4 Non-serious US VAERS Reports after Gardasil Among Children 9 ≤ 16 Years

Most Frequently Coded Terms in VAERS GARDASIL Non-Serious Reports among Children 9 to 16 Years

MedDRA Preferred Term	Number of Events	Listed in Label
Dizziness	406	Yes
Syncope	364	Yes
Headache	254	Yes
Nausea	203	Yes
Injection site erythema	188	Yes
Loss of consciousness	188	Yes
Pallor	187	(Presyncope)
Injection site swelling	164	Yes
Pyrexia	142	Yes
Erythema	134	Yes
Vomiting	134	Yes
Injection site pain	131	Yes
Fall	124	Syncope sometimes resulting in falling with injury

Most Frequently Coded Terms in VAERS GARDASIL Non-Serious Reports

Among Male Children 9 to 16 Years

MedDRA Preferred Term	Number of Events	Listed in Label
Dizziness	87	Yes
Syncope	67	Yes (Highlighted)
Injection site erythema	59	Yes
Injection site swelling	46	Yes
Pallor	41	"presyncope"
Headache	34	Yes
Nausea	33	Yes
Loss of consciousness	31	"Syncope"
Pyrexia	31	"fever"
Injection site pain	27	Yes
Erythema	26	Yes
Fall	26	"syncope sometimes resulting in falling with injury"

The non-serious reports describe labeled and expected events after vaccination. The types of non-serious reports are similar for males and females. Syncope is a common serious and non-serious reported post-vaccination adverse event.

7.5 VAERS reports for 0- 8 year old children

There were 21 reports in VAERS for 0-8 year olds having received Gardasil, although it is only licensed for 9-26 year olds. The reports were all non-serious, 20 were domestic and one was foreign. 13 were in females and 8 in males. The ages of the Gardasil recipients ranged from 0 to 6 years. Three of the patients were administered all of the three adolescent vaccines (Menactra, TdaP and Gardasil) even though their birth dates confirmed that they were under 6 years of age. Twelve reports specifically described medication/administration errors and no adverse events. Other reports described adverse events including presyncope, syncope, injection site reaction, vomiting, rash.

8. PLANNED AND ONGOING POSTMARKETING STUDIES

"Post-Licensure Observational Study of the Safety of Gardasil in Males"
is a planned study that will build upon the large post-marketing study completed in females and will be implemented in the Kaiser Permanente Southern California (KPSC). The study population is targeted to include 9-26 y/o males, 135,000 with at least one dose and 44,000 completing the 3 dose series. An autoimmune cohort, which must have been registered with KPSC for 12 months prior to vaccination, will also be analyzed. The study will end when targets are reached, or 6 years after study date. This study will also focus on syncope after vaccination.

Merck's pregnancy registry is ongoing and should be finalized in 2012.

VSD plans to begin a study on Gardasil in males when administration in this population is sufficient. The pre-specified endpoints will be similar to the study conducted in females unless any new safety signals arise before the beginning of this study. Currently, the low rate of uptake among males precludes a VSD rapid cycle analysis study.

FDA's ongoing and planned postmarketing surveillance includes continued passive surveillance for serious and unexpected adverse events using VAERS. In addition, FDA will conduct a large study in Mini-Sentinel to evaluate VTEs after Gardasil. The Post-licensure Rapid Immunization Safety Monitoring (PRISM) component of Mini-Sentinel evolved from the Post-licensure Rapid Immunization Safety Monitoring (PRISM) system developed for monitoring the safety of the H1N1 monovalent vaccine. It is an active surveillance system linking vaccination and subsequent health outcomes data from state vaccine registries and large health plans. The Mini-Sentinel project will include data from HealthCore, Humana, and Aetna through the Harvard Pilgrim Health Care Institute. This study will assess the occurrence of VTEs after vaccination with Gardasil, verify the ICD-9 codes for VTEs, and evaluate OCPs as a confounding factor and identify if there is interaction between the vaccine and any of the known risk factors for VTEs.

9. CONCLUSIONS

Over 15 million doses of Gardasil were distributed in the US between October 16, 2009 and December 22, 2011. More than 600,000 doses have been actively monitored since licensure in the Vaccine Safety Datalink. Merck completed an observational PMC in over 346,972 doses of Gardasil administered to 189,629 females. There are no new safety concerns for Gardasil. Syncope continues to be identified as an important safety concern, and the label was previously updated to communicate this issue. FDA and CDC continue efforts to improve public and health care provider awareness and prevention of post-vaccination syncope, including convulsive syncope and injuries from falls. Venous thromboembolism has been reported and observed after Gardasil; however, there are significant confounding factors which are known to cause blood clots including: oral contraception, smoking, obesity, coagulation disorders. Further investigations using more sophisticated research methods are being conducted by the VSD and FDA's Mini-Sentinel Initiative. Merck is planning and conducting additional postmarketing studies with safety endpoints, including a second large active surveillance study of 135,000 doses of Gardasil in males. The Vaccine Safety Datalink plans to do a study in males as well when vaccine uptake in this popualtion increases. Studies continue to evaluate autoimmune diseases occurring after vaccination, with an analysis also planned in males. FDA recommends continued safety monitoring of Gardasil.

10. REFERENCES

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